REMARKS

Claim 14-19 and 29-31 are pending in the present application, including independent claim 14. Independent claim 14, for instance, is directed to a flow-through assay device for detecting the presence or quantity of an analyte residing in a test sample. The flow-through assay device comprises a porous membrane in communication with optical detection probes conjugated with a first antibody specific for the analyte. The porous membrane defines a competitive zone and a detection zone. The competitive zone contains a second antibody immobilized on the porous membrane that is complexed to an antigen containing an optically detectable substance prior to the application of a test sample to the device. The antigen is identical to or an analog of the analyte and the optically detectable substance is capable of producing a competitive signal when contained within said competitive zone. The detection zone contains a third antibody that is configured to bind to complexes formed between the analyte and the conjugated optical detection probes to produce a first detection signal. The third antibody is also configured to bind to the antigen from the competitive zone to produce a second detection signal, wherein the amount of the analyte within the test sample is determined from said competitive signal, and at least one of the first detection signal and the second detection signal.

To better understand what is required by the present claims, reference is made to Figs. 4-5 of the specification (portions of which are reproduced below), which illustrate one embodiment of the present invention.

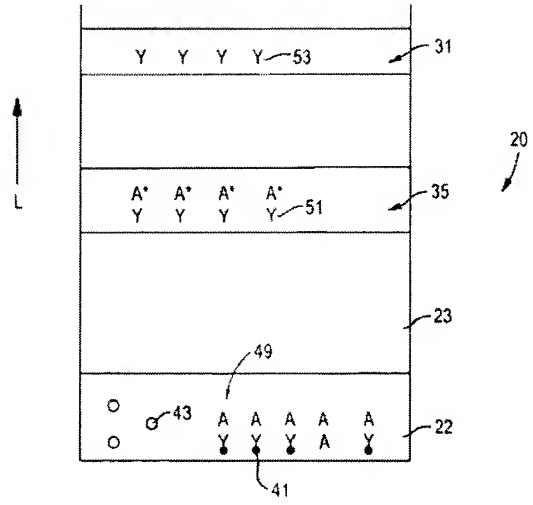

FIG. 4

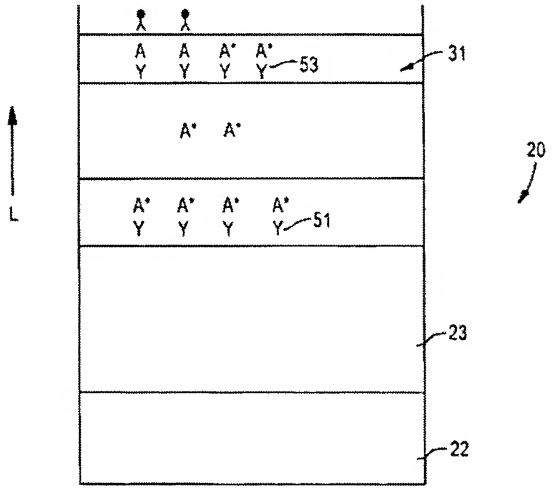

FIG. 5

As shown in Fig. 4, a test sample containing an antigen A travels in the direction "L" and mixes with fluorescent detection probes 41 conjugated with an antibody. The antigen A binds with the probes 41 to form analyte/conjugated probe complexes 49. Some of the antigen A remains free due to the limited availability of the probes 41. As shown in Fig. 5, the free antigen A and the complexes 49 then travel to the competitive

zone 35, within which is immobilized an antibody 51 complexed to a labeled molecule A* that is identical in nature or an analog of the antigen A. Due to its smaller size, the free antigen A reaches the competitive zone 35 first, and competes with the molecule A* for the binding sites on the antibody 51. The complexes 49 and the displaced molecules A* travel on to the detection zone 31 and bind to an antibody 53. Once captured, the fluorescence signals of the labeled molecules A* and detection probes 41 may be measured at the detection zone 31 and the competitive zone 35.

Figs. 3A and 3B (reproduced below) show one relationship of the signal intensity of the fluorescent detection labels of Figs. 4 and 5 (A* and the detection probes 41) for both the competitive zone 35 and the detection zone 31.

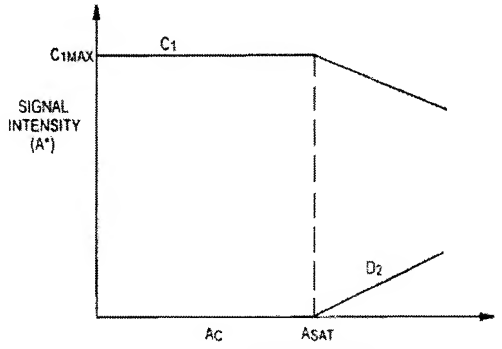

FIG. 3A

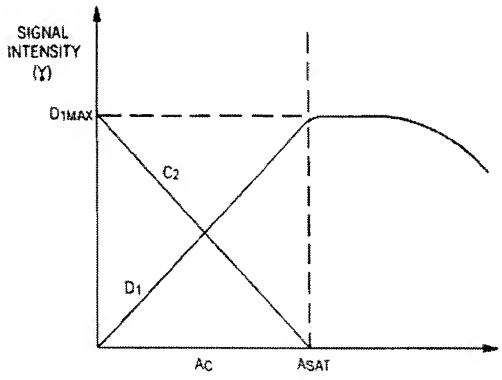

FIG. 3B

As shown, when no analyte A is present in the test sample, the labeled antigen A* produces a first competitive signal ("C_1") at the competitive zone 35 that is constant at its maximum value, C_{1max}. Further, the conjugated detection probes 41 bind to the antigen A* within the competitive zone 35, thus producing a second competitive signal ("C_2"). No signals exist at the detection zone 31. As the concentration of the analyte A increases, it begins to form the complexes 49 with the conjugated detection probes 41. Because the complexes 49 no longer possess an epitope capable of binding with the antigen A*, they travel past the competitive zone 35 and bind to the antibody 53 at the detection zone 31. This causes a decrease in the second competitive signal "C_2", and also causes the production of a first detection signal "D_1" at the detection zone 31. The intensity of the second competitive signal "C_2" continues to decrease and the intensity of the first detection signal "D_1" continues to increase until the concentration of the analyte A exceeds the amount of available conjugated detection probes 41, which is designated in Figs. 3A and 3B as "A_{sat}."

At "A_{sat}", the free analyte A travels to the competitive zone 35. Because it is generally smaller in size, the free analyte A typically reaches the competitive zone 35 before the complexes 49. Thus, within the competitive zone 35, the free analyte A begins to compete with the labeled antigen A* for the binding site of the antibody 51. Without intending to be limited by theory, the present inventors believe that the ability to replace the antigen A* with the free analyte A from the test sample may help extend the detection range of the assay. Namely, when the free analyte A begins to compete with the antigen A* for binding sites at the competitive zone 35, the intensity of the first competitive signal "C_1" begins to decrease due to a loss in the labeled antigen A* (Fig.

3A). This decrease is proportional to the amount of analyte A exceeding the analyte saturation concentration "A_{sat}" and the binding capacity of the conjugated detection probes 41. Moreover, at the analyte saturation concentration "A_{sat}", the intensity of the second competitive signal "C_2" is zero as all of the available conjugated detection 41 probes are used to form the complexes 49, and thus, bypass the competitive zone 35 (Fig. 3B).

Further, at the analyte saturation concentration "A_{sat}", all of the conjugated detection probes 41 form complexes 49 that ultimately bind to the detection zone 31. Thus, the intensity of the first detection signal "D_1" reaches its maximum value, designated "D_{1max}". This value is predetermined and known because the amount of the detection probes 41 is selected to correspond to the amount of the available antibody 53 at the detection zone 31. Although the first detection signal "D_1" reaches its maximum intensity at the analyte saturation concentration "A_{sat}", a second detection signal "D_2" begins to be produced. This second detection signal "D_2" is a result of the labeled antigen A* being replaced at the competitive zone 35 and traveling to the detection zone 31, where it and the conjugated detection probes 41 become immobilized. In this manner, the second detection signal "D_2" increases, while the first detection signal "D_1" actually decreases. In most instances, the signal "D_2" should also be proportional to the difference in the signals "C_{1max}" and "C_1." It should be also understood that, due to the equilibrium conditions at the competitive zone 35, a small portion of free analyte A from the test sample may bind at the detection zone 31. Although this free analyte A is not detectable, it is believed to be insignificant in

comparison to the amount of free analyte A that would otherwise be present in the absence of the competitive zone 35.

In the Office Action, claims 14-16 were rejected under *35 U.S.C. 103(a)* as being obvious over U.S. Patent No. 7,144,742 to Boehringer, et al. in view of U.S. Patent No. 5,573,921 to Behnke, et al. An illustrative embodiment of the lateral flow device of Boehringer, et al. is shown in Fig. 4. As shown, the device contains a labeling zone 14, barrier zone 16a, and detection zones 16b, 16c, and 16d. In this embodiment, the labeling zone 14 has a biotinylated anti-analyte mouse IgG antibody, the barrier zone 16a contains an analyte or analyte analogue, and the detection zones contains antibodies or streptavidin of different affinities. As sample analyte concentration increases, a greater amount of the antibody from the labeling zone ("first sbp member") will form complexes with the sample analyte and thus pass through the barrier zone and become captured in the detection zones.

The Office Action likened this "barrier zone" to the "competitive zone" of independent claim 14. Although the barrier zone does contain an analyte or an analyte analog, this is where any similarity with the competitive zone of claim 14 ends. More specifically, the competitive zone of claim 14 also contains "a second antibody" and requires that the "antigen" is "complexed" thereto. Furthermore, the antigen within the competitive zone contains "an optically detectable substance prior to the application of a test sample." None of these features are possessed by the barrier zone of Boehringer, et al.

Behnke, et al. was nevertheless cited in the Office Action as teaching that an antibody complexed to an antigen. Referring to Fig. 1a of Behnke, et al., the test strip 1

includes antibody molecules 3 in a measurement area 2 and a tracer 4 that contains the analyte 5 and an appendage 6 (e.g., biotin) bound to the antibody molecules 3. When dipped into a test solution (Fig. 1b) containing the analyte 5 and reaction partner 9 (e.g., streptavidin-enzyme conjugate), each molecule of the analyte 5 can displace one tracer molecule 4. The displaced tracer 4 binds to the reaction partner 9 and migrates into an area 11 of the test strip located above the measurement area 2. The test strip 1 is then dipped into another vessel 12 containing a developing solution 13 (Fig. 1c). The solution 13 contains substrate molecules 14 that enter the test strip 1 and react to form a dye 17.

As indicated above, Behnke, et al. does generally describe an antibody bound to an analyte analog (tracer). On this basis, the Office Action argues that it would have been obvious to combine this aspect with Boehringer, et al. because Behnke, et al. teaches the benefit of binding an analyte analog attached to a dye to an immobilized antibody so that "the bound analyte analog attached to the dye allows for directly visualizing the area of the test strip comprising the immobilized antibody (i.e., barrier zone) even before beginning the test." This rationale for combining the references, however, is completely misplaced and contrary to the teachings of the references. The purpose of Boehringer, et al., as explained above, is to include a "barrier zone" that exhibits a signal when the analyte concentration is either high or low and a "detection zone" for quantization of the analyte. If Boehringer, et al. were to be modified include an antibody/antigen complex at the "barrier zone", it would completely fail to fulfill its intended function because it would no longer be able to bind to the labeled binding member ("first sbp member"). Applicants also submit that no perceived benefit would

exist for "visualizing the area of the test strip even before beginning the test" as suggested by the Office Action. In any event, the systems of Behnke, et al. and Boehringer, et al. are so vastly different from each other that one of ordinary skill in the art would have possibly found it obvious to make the combination proposed in the Office Action.

Applicants emphasize that an invention is not obvious simply because various parts of the claims may be found somewhere in the prior art. If this were the case, virtually every invention would be considered obvious. Instead, the proper standard under *§ 103* is whether the claimed invention *as a whole* when viewing the teachings of the references *in their entirety*. In this case, as explained above, the present claims are so substantially different from the references, when properly viewed in their entirety, that one of ordinary skill in the art would not have conceivably modified and/or combined the references as suggested in the Office Action.

As a final note, Applicants respectfully request rejoinder of the withdrawn method claims 20-28 if the remaining claims are otherwise allowable.

It is thus believed that the present application is in complete condition for allowance and favorable action, therefore, is respectfully requested. Examiner DiRamio is invited and encouraged to telephone the undersigned, however, should any issues remain after consideration of this Amendment.

Please charge any additional fees required by this Amendment to Deposit Account No. 04-1403.

Respectfully requested,

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4/11/08
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